General

Guideline Title

Radionuclide therapy for neuroendocrine malignancies.

Bibliographic Source(s)

Gulenchyn KY, Yao X, Asa SL, Singh S, Law C, Radionuclide Therapy for Neuroendocrine Tumours Expert Panel. Radionuclide therapy for neuroendocrine malignancies. Toronto (ON): Cancer Care Ontario (CCO); 2011 Aug 15. Various p. (Evidence-based series; no. 12-13). [90 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

The Expert Panel and the Working Group offer the following recommendations based on the evidence reviewed:

- Peptide receptor radionuclide therapy (PRRT) appears to be an acceptable option in adult patients with neuroendocrine cancer who are inoperable, have residual disease following surgery or other ablative therapy, or have metastases. PRRT is relatively safe and well tolerated with renal protection using lysine and arginine amino acid solution, especially for ^{90}Y-DOTALAN and ^{177}Lu-DOTATATE. However, renal function must be monitored.
- Treatment with PRRT in Ontario should be conducted as part of one or more randomized controlled trials (RCTs), or in large comparative clinical trials if an RCT is not feasible, under the authority of a Clinical Trials Agreement, to clarify the further effects of PRRT (for example, comparing ^{177}Lu-DOTATATE with sunitinib in an RCT).
- ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) may be effective for malignant neuroblastoma, paraganglioma, or pheochromocytoma, but there is insufficient evidence to suggest its efficacy for adult neuroendocrine carcinoma patients. However, the hematologic toxicity, severe infections, and secondary malignancies possible afterwards should be considered.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Neuroendocrine tumours (NETs)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Endocrinology

Neurology

Nuclear Medicine

Oncology

Radiation Oncology

Radiology

Intended Users

Physicians

Guideline Objective(s)

- To evaluate what the effects of the eight commonly used and studied therapeutic radiopharmaceuticals described in Table 1 in the original guideline document are in patients with different types of neuroendocrine malignancies
- To evaluate which one of the eight therapeutic radiopharmaceuticals is most effective in improving clinical outcomes (i.e., tumour response, duration of tumour response, overall survival [OS] time/rate, progression-free survival [PFS] time/rate, biochemical response, and quality of life [QOL]) in patients with different types of neuroendocrine malignancies
- To evaluate what the toxicities are for each therapeutic radiopharmaceutical

Target Population

Neuroendocrine cancer patients who are inoperable, have residual disease following surgery or other ablative therapy, or have metastases

Interventions and Practices Considered

1. Peptide receptor radionuclide therapy (PRRT)
2. Renal protection (lysine and arginine amino acid solution)

3. ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG)

Major Outcomes Considered

- Tumour response
- Duration of tumour response
- Overall survival (OS) time/rate
- Progression-free survival (PFS) time/rate
- Biochemical response
- Quality of life (QOL)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

A literature search was performed using MEDLINE and EMBASE through the Ovid search engine from January 1, 1998, to November 4, 2010. The search strategies are reported in Appendices 2 and 3 in the original guideline document. The following resources were checked for existing systematic reviews and practice guidelines: the Cochrane Library (to Issue 10, 2010) and the Standards and Guidelines Evidence Inventory of Cancer Guidelines (referred to below as the Inventory), which included guidelines identified in and/or published by the National Guideline Clearinghouse, the National Health and Medical Research Council (Australia), the New Zealand Guidelines Group, the Canadian Medical Association Infobase, the American Society of Clinical Oncology, the National Comprehensive Cancer Network, the European Society for Medical Oncology, and the European Neuroendocrine Tumour Society, among others. Over 1100 English-language cancer control guidelines and standards released from 2003 through June 2010 were available in the Inventory when it was checked on October 18, 2010.

Study Selection Criteria

Inclusion Criteria

Articles were eligible for inclusion in this systematic review if they were:

1. Full text reports published from January 1, 1998, to November 4, 2010.
2. Clinical practice guidelines based on a systematic review, systematic reviews, randomized trials, prospective studies, or retrospective studies that reported on at least one clinical outcome.
3. Prospective studies that had ≥30 patients. This number was considered the minimum number of subjects on which results could be reported with enough certainty (e.g., narrow enough 95% confidence intervals [CIs]) such that the data could be used in the formulation of recommendations.
4. Retrospective studies that had ≥100 patients. This number is greater than that chosen for prospective studies because retrospective studies have a greater potential for bias and thus can be more difficult to interpret.
5. Studies that included malignant neuroendocrine tumours (NET) patients who were inoperable or who had residual disease or metastases (patients could have been treated with prior systemic therapy).
6. Studies that reported or compared the effects of any of eight therapeutic radiopharmaceuticals listed in Table 1 in the original guideline documents on any of the following clinical outcomes: complete response (CR), partial response (PR), minor response (MR), stable disease (SD), duration of response (DR), progression-free survival (PFS), overall survival (OS), biochemical response, quality of life (QOL), and toxicity.

Exclusion Criteria

Articles were excluded if they met any of the following criteria:

1. Were published in a language other than English
2. Were non-systematic reviews, case reports, animal studies, letters, editorials or commentaries
3. Recruited only patients with small-cell lung cancer (SCLC)
4. Did not report any outcomes after radionuclide therapy (RT) in which systemic therapy was immediately followed RT

The reference lists of the included articles were hand searched, and no further eligible papers were found.

Number of Source Documents

Thirty-two articles were included in this systematic review.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Synthesizing the Evidence

If possible, meta-analyses of each trial outcome would be considered and conducted. The subgroup data with a denominator less than 10 were not reported because a sample size <10 is considered a case report. Any data for which denominators were <30 should be considered carefully because they usually have extremely large 95% confidence interval (CIs) and are unlikely to be statistically significant.

STATA 11.0 would be the statistical software for statistical calculation purposes and for producing figures. A two-sided significance level of $\alpha = 0.05$ was assumed.

Study Quality

The 24 included studies were assessed for quality (see Table 4 in the original guideline document), according to the Newcastle-Ottawa Scale used in non-randomized studies (NRS) method group workshops of the Cochrane Collaboration to illustrate issues in data extraction from primary NRS.

Outcomes

Meta-analyses of the trial results for tumour response rates on imaging and/or survival time/rates were not feasible. The various clinical centres differed in radionuclide therapy (RT) interventions, doses and treatment schema for the same intervention, patient characteristics, neuroendocrine tumour (NET) types, tumour status at baseline, and criteria for evaluating tumour response, making meaningful results from pooling impossible. Meta-analyses of outcomes for biochemical response, quality of life (QOL), and/or toxicity were also not feasible because of the differences in outcome assessment measurement and timing.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Methods

The evidence-based series guidelines developed by the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO), use the methods of the Practice Guidelines Development Cycle. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by four members of the Radionuclide Therapy (RT) in Neuroendocrine Tumour (NET) Working Group and one methodologist of the PEBC. All data were audited by a second, and independent, person.

The systematic review is a convenient and up-to-date source of the best available evidence on RT for patients with malignant NETs.

Radionuclide Therapy for Neuroendocrine Tumours Expert Panel Conference

On March 4, 2011, the draft guideline was presented to members of the Radionuclide Therapy for Neuroendocrine Tumours Expert Panel. This guideline contained draft recommendations that had been crafted by the Working Group. There was no strong disagreement regarding these draft recommendations or evidentiary base. It was suggested that several recommendations be reworded into more action-oriented language, and that the order and classification of the recommendations and qualifying statements be changed somewhat to highlight the most important issues.

Some members of the Expert Panel did express concern with respect to the study selection criteria, specifically the sample size limits (i.e., ≥30 for prospective studies and ≥100 for retrospective studies). There was concern that retrospective studies with sample sizes of less than 100 may provide some valuable information not currently included.

Based on the Expert Panel's feedback, the Working Group members revised the recommendations in the guideline and the conclusion of the evidentiary base. As the time available for the completion of this guideline was limited, the Working Group decided to submit the updated draft to the Report Approval Panel (RAP) for review. At the same time, retrospective studies with sample size between 30 and 100 would be reviewed and the results provided in an appendix after RAP review.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Program in Evidence-based Care (PEBC) Director's Review

Following the presentation of this evidence-based series (EBS) draft report for Expert Panel review, the report was reviewed and approved by the director of the PEBC, Dr. Melissa Brouwers, with expertise in methodologic issues.

In response to the RAP review feedback, all the raised points were revised by the Working Group.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two pronged and includes a targeted peer review intended to obtain direct feedback on the draft report from

a small number of specified content experts and a professional consultation intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Guideline Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC RAP, the guideline authors circulated Sections 1 and 2 to external review participants for review and feedback.

Methods

Targeted Peer Review

During the guideline development process, 11 targeted peer reviewers from the world considered to be clinical and/or methodological experts on the topic were identified by the guideline authors. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Four reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on April 29, 2011. Follow-up reminders were sent at two weeks and at four weeks. All the targeted peer reviewers were required to complete the conflict of interest form.

Professional Consultation

One hundred four potential participants were identified by the guideline authors. Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Participants were asked to rate the overall quality of the guideline (Section 1 in the original guideline document) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1 in the original guideline document) and the evidentiary base (Section 2 in the original guideline document). The notification email was sent on May 3, 2011. Two follow-up reminders were sent on May 19 and May 31, 2011.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Radionuclide Therapy for Neuroendocrine Tumours Expert Panel and the Working Group.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by prospective trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Peptide Receptor Radionuclide Therapy (PRRT)

- Fifteen prospective single-arm articles and one prospective comparative study met the study selection criteria; of the nine published after 2005, all investigated the effects of ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, or ^{177}Lu-DOTATATE. The total sample size was 1179. All the patient tumours showed a higher or the same uptake on octreoscan than on liver uptake before PRRT. All but one study reported the overall response rate as determined by three different imaging criteria in a variety of stage III-IV neuroendocrine tumour (NET) subgroups. Across all agents, overall response rates ranged from 5% to 75% in various tumour subgroups, with wide 95% confidence intervals (CI).
- Three studies were conducted in the same clinical centre to investigate the effects of ^{111}In-DTPAOC, ^{90}Y-DOTATOC, and ^{177}Lu-DOTATATE at different time periods. The median overall survival (OS) and progression-free survival (PFS) time was 37 and 14 months, respectively, for ^{90}Y-DOTATOC at five-year follow-up, and 46 and 33 months, respectively, for ^{177}Lu-DOTATATE at four years. The

overall response rate was 18% (CI, 6% to 30%) for patients with progressive stage III-IV NET treated with ^{111}In-DTPAOC, 21% (CI, 11% to 31%) for patients with stage III-IV neuroendocrine gastroenteropancreatic tumours (GEP-NET) treated with ^{90}Y-DOTATOC, and 46% (CI, 40% to 52%) for patients with stage IV GEP-NET disease treated with ^{177}Lu-DOTATATE.

- Eight of the 16 articles reported survival outcomes, with six reporting median OS times ranging from 15 to 46 months for various stage III-IV NET subgroups. There was no significant difference in OS time between the intervention (14 patients treated with ^{111}In-DTPAOC and five patients treated with ^{131}I-metaiodobenzylguanidine [^{131}I-MIBG]) and control arm in the unique comparative trial.

^{131}I-MIBG Therapy

- Six prospective single-arm, one retrospective comparative, and one retrospective single-arm study examining the effectiveness of ^{131}I-MIBG were eligible; the total sample size was 612. All the patients showed at least one lesion as positive on the ^{123}I-MIBG or ^{131}I-MIBG scintigraphy. The overall tumour response rate on imaging by various imaging criteria ranged from 32% to 75% for stage III-IV pediatric neuroblastoma patients with a median age of 2.0 to 6.6 years old (19-23) and was 26% for adult and stage III-IV NET patients (including 22 neuroblastomas, 10 pheochromocytomas, three paragangliomas, six medullary thyroid carcinomas, and four carcinoids) and 27% for patients with stage IV paraganglioma or pheochromocytoma.
- The Sywak et al. study was the unique comparative study for comparing standard therapies alone with standard therapies plus ^{131}I-MIBG in stage IV patients with midgut carcinoid. The OS rate was 63% (CI, 47% to 75%) in the intervention group and 47% (CI, 34% to 59%) in the control group at five years, without statistical significance (p=0.10).

Potential Harms

Peptide Receptor Radionuclide Therapy (PRRT)

Of the fifteen articles that reported on toxicity, 11 specified one of two criteria used for grading toxicity. Nausea and vomiting were common during therapy. The severe toxicities included the following: for ^{111}In-DTPAOC, 8% of patients developed myelodysplastic syndrome (MDS) and/or leukemia in one study; for ^{90}Y-DOTATOC, 0.9% to 3.4% of patients developed grade 4 renal toxicity in three studies, with 2% of patients developing MDS in one study; for ^{90}Y-DOTALAN, no severe toxicity was found in one study; for ^{90}Y-DOTATATE, 30% of patients developed grade 2 renal toxicity at two years in one study; and for ^{177}Lu-DOTATATE, 0.6% of patients developed hepatic insufficiency, 0.8% developed MDS, and 0.4% developed renal insufficiency in one study. For studies investigating the effects of ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, and ^{177}Lu-DOTATATE, lysine and arginine amino acid solution was infused to protect kidney function.

^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) Therapy

Of seven studies reporting on toxicity, three used different criteria, and four studies did not specify the criteria for toxicity grading. Hematologic toxicities were the main severe side effects. Forty-three percent of patients had bone marrow replacement (BMR), and one patient developed secondary leukemia in one study. Five percent of patients in one study and 2% of patients in another study developed leukemia or MDS. In a retrospective study, five (4%) three- to five-year-old neuroblastoma patients developed secondary malignancies after ^{131}I-MIBG therapy either as part of first-line therapy or as salvage therapy for resistant or recurrent disease: one acute nonlymphoblastic leukemia at one and a half years, one chronic myelomonocytic leukemia at four years, one malignant schwannoma at seven years, one rhabdomyosarcoma at 14 years, and one angiomatoid malignant fibrous histiocytoma at 10 years after ^{131}I-MIBG. In a fifth study, 39% of patients needed autologous BMR, and 9% of patients died where ^{131}I-MIBG was utilized as the first-line treatment. Forty-one percent of patients had grade 2-3 hematologic toxicities in a sixth study. After an accumulative dose of at least 63.3 gigabecquerels (GBq) ^{131}I-MIBG therapy, 4% of patients who did not have prior radiation or chemotherapy developed MDS and acute myeloid leukemia at two and five years, respectively, in the seventh study. In addition, 4% of patients in that same study developed acute respiratory distress syndrome, 4% developed bronchiolitis obliterans organizing pneumonia, and 2% had a pulmonary embolism.

Qualifying Statements

Qualifying Statements

- There is limited evidence, based on a historical comparison of studies from a single centre (see key evidence in the original guideline document), that ^{177}Lu-DOTATATE may be associated with greater overall survival (OS), progression-free survival (PFS), and overall response rate (defined as the sum of complete response, partial response, and minor response rates) compared with ^{90}Y-DOTATOC or ^{111}In-DTPAOC. Therefore, ^{177}Lu-DOTATATE would be an appropriate agent to include in the future clinical trials described in the original guideline document.
- Prior to the administration of therapy, the tumours from neuroendocrine tumour (NET) patients who are to receive peptide receptor radionuclide therapy (PRRT) or ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) should demonstrate a positive uptake of the related diagnostic agent.
- A recommendation cannot be made for or against the use of PRRT in early-stage NET patients, as there is no relevant evidence.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Gulenchyn KY, Yao X, Asa SL, Singh S, Law C, Radionuclide Therapy for Neuroendocrine Tumours Expert Panel. Radionuclide therapy for

neuroendocrine malignancies. Toronto (ON): Cancer Care Ontario (CCO); 2011 Aug 15. Various p. (Evidence-based series; no. 12-13). [90 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Aug 15

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Guideline Committee

Radionuclide Therapy for Neuroendocrine Tumours Expert Panel

Composition of Group That Authored the Guideline

Expert Panel Members: Dr. Leonard Kaizer, Medical Oncologist, Peel Regional Cancer Centre, Mississauga, Ontario; Dr. Travis Besanger, Head of Quality Assurance and Quality Control, Centre for Probe Development and Commercialization, Hamilton, Ontario; Dr. Daryl Gray, Surgical Oncologist, London Health Sciences Centre London, London, Ontario; Dr. Barry Ivo, Radiation Safety Office, University of Toronto, Toronto, Ontario; Dr. Eugene Leung, Nuclear Medicine Physician, Department of Nuclear Medicine, The Ottawa Hospital, Ottawa, Ontario; Dr. Robyn Pugash, Interventional Radiologist, University of Toronto, Toronto, Ontario; Dr. Robert (Robin) Reid, Associate Professor, Nuclear Medicine Physician, Victoria Hospital, London, Ontario; Dr. Rebecca Wong, Department of Radiation Oncology, Princess Margaret Hospital, Toronto, Ontario; Ms. Maureen Coleman, patient representative, Ontario

Working Group Members: Dr. Karen Gulenchyn, Chief of Department of Nuclear Medicine, Hamilton Health Sciences, Hamilton, Ontario; Dr. Sylvia Asa, Pathologist-in-chief, University Health Network, Toronto, Ontario; Dr. Calvin Law, Associate Professor, Department of Surgery, University of Toronto, Toronto, Ontario; Dr. Simron Singh, Medical Oncologist, Neuroendocrine Clinic, Sunnybrook Health Sciences, Toronto, Ontario; Ms. Xiaomei Yao, Research Coordinator, Program in Evidence-based Care, Cancer Care Ontario, Hamilton, Ontario

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, Expert Panel members, and internal and targeted external reviewers were asked to disclose potential conflicts of interest. Three guideline authors declared they had no conflicts. Two others (S. Singh and C. Law) declared conflicts and reported receiving more than $5000 in a single year from consulting fees, honoraria, and/or other support from Novartis and Pfizer pharmaceutical companies. Both these authors also declared that they had received

research grant support from Novartis.

For the Expert Panel, seven members declared they had no conflicts of interest, and two (T. Besanger and R. Reid) declared conflicts. TB reported receiving employment income from a previous employer, Molecular Insight Pharmaceuticals, a clinical developer of ^{90}Y-DOTATOC and ^{131}I-MIBG. RR reported receiving more than $5000 in a single year for travel expenses and research funding (now completed) from Novartis for his department for database development.

The PEBC Director (M. Brouwers) and the PEBC Assistant Director (H. Messersmith) declared that they had no COI.

For the targeted external reviewers, two declared they had no COI, and one (R. Lebtahi) declared conflicts. RL was the co-author in the European Neuroendocrine Tumour Society (ENETS) guideline, and he will be a principal investigator for a multicentre trial about ^{111}In-DTPAOC therapy in front of curative intent after complete resection of liver metastases in patients with neuroendocrine tumours (NETs) in France at the end of 2011 year.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca.

Guideline Status

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Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

Availability of Companion Documents

The following are available:

- Radionuclide therapy for neuroendocrine malignancies. Summary. Toronto (ON): Cancer Care Ontario (CCO). 2011 Aug 15. 8 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario (CCO) Web site .
- Program in Evidence-Based Care (PEBC) handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Electronic copies: Available in PDF from the CCO Web site.

Patient Resources

None available

NGC Status

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